SYNTHESIS OF SOME PHARMACOLOGICAL ACTIVE SCHIFF BASE, FORMAZAN, THIAZOLIDINONE AND AZETIDINONE DERIVATIVES.

A Schiff base named after German chemist Hugo Schiff, is a compound having a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group, not hydrogen.[1] Schiff bases have general formula $R^1R^2C=NR^3$, where R is an organic side chain. Schiff base is synonymous with azomethine. Some restrict the term to the secondary aldimines (azomethines where the carbon is connected to a hydrogen atom), thus with the general formula RC=NR'. [2] The chain on the nitrogen makes the Schiff base a stable imine. A Schiff base derived from an aniline, R^3 is a phenyl or a substituted phenyl, can be called an anil.[3] Several studies revealed that the presence of a lone pair of electrons in an sp2 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance.[4-10] Because of the relative ease of preparation, Synthetic Flexibility and the special property of C=N, Schiff bases are excellent Chelating agents[11-14], especially when a functional group like –OH or –SH is present close to the azomethine group so as to form a five or six membered ring with metal ion. Schiff bases are known to show a wide range of diverse pharmacological activities such as antimicrobial [15], antimalarial [16], anticancer [17], antibacterial [18], antifungal [19], antitubercular [20], anti-inflammatory [21], antiviral [22], anti-HIV [23], catalytic [24], Cytotoxic [25], lipoxygenase inhibitor [26] and antioxidant [27].

2-Azetidinones, commonly known as β-lactums, are well known heterocyclic compounds among organic and medicinal chemists [28-32] since it forms a part of the antibiotic molecules. The most widely used antibiotics such as Penicillins, Nocardicins, Cephalosporins contains the β-lactum ring. Recently, some other types of biological activities besides the antibacterial activity have been reported in compounds containing 2-azetidinone ring [33, 34]. Such biological activities include anti-tubercular [35, 36], antifungal [37, 38], anticonvulsant [39], anti-inflammatory [40], analgesic [41], CNS depressant Activity [42], antimicrobial [43, 44], and antiviral[45].

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulphur and nitrogen in a five member ring. A lot of research work on thiazolidinones has been carried out in the past. The nucleus is also

known as wonder nucleus because it gives out different derivatives with all different types of biological activities.4-Thiazolidinones have attracted considerable attention as they are well endowed with diverse range of pharmaceutical activities. The presence of N-C-S linkage in these compounds has been shown to have antimicrobial[46, 47], anti-HIV[48], antifungal[49],antitubercular[50], antioxidant[51], anti-inflammatory[52], anticonvulsant[53], anthelmintics[54], antidiabetic[55], Pesticidal[56], antidiarrheal[57], antihistaminic[58], cycloxygenase inhibitory[59] and cardio protective[60] properties.

The formazan derivatives of Schiff bases have found wide applications, not only as pharmacological agents but also as dyeing[61] and chelating agents[62]. Formazans form tetrazolium salts when they are oxidized [63]. Tetrazolium salts are reduced back to formazans by the enzymes in the cell and stain tissue. The tetazolium- formazan system is classified as a marker of vitality [64] and this feature enables the determination of activity in tumour cells. Formazans and heterocyclic hydrazones are known for their wide spectrum of biological activities such as antiviral [65], antimicrobial [66, 67], anti- HIV [68], anticancer [69, 70], antifungal [71] and anti-inflammatory [72].

Piperazine is an interesting heterocyclic moiety as constituent of several biologically active molecules. The polar nitrogens in the piperazine ring confer bioactivity to molecules and enhance favourable interaction with macromolecules [73, 74]. Piperazinyl-linked ciprofloxacin dimmers are potent antibacterial [75] agents and potential antipsychotic agents [76]. Piperazine derivatives containing tetrazole nucleus have been reported as antifungal agents [77]. Most of the quinoline drugs, such as norfloxacin and ciprofloxacin having piperazine nucleus have shown broad spectrum activity against respiratory, urinary, gastrointestinal tract, skin and soft tissue infections caused by bacteria [78]. Various cyanopiperazine derivatives have been known for their use in the synthesis of pharmaceutical intermediates, peptide analogues and antibacterial drugs [79, 80, and 81]. Besides these activities, piperazines have also been found to possess anti-histaminic [82], analgesic [83], anti-inflammatory [84], anti-HIV [85], antimalarial [86], antitubercular [87], antimicrobial [88, 89]. Thus, keeping in view the wide range of biological activities shown by piperazine molecule, we planned to prepare various Schiff base, thiazolidinone, azetidinone and formazan derivatives, taking N-ethylpiperazine as a starting building block and study the microbial activities of the mentioned derivatives.

The thesis will consist of five chapters:

Chapter I: Introduction and literature review of Schiff base, synthesis of Schiff base derivatives from N-ethylpiperazine, physical properties, spectral studies and microbial activity studies.

Chapter II: Introduction and literature review of 4-thiazolidinones, synthesis of 4-thiazolidinones derivatives from N-ethylpiperazine, physical properties, spectral studies and microbial activity studies.

Chapter III: Introduction and literature review of 2-azetidinones, synthesis of 2-azetidinone derivatives from N-ethylpiperazine, physical properties, spectral studies and microbial activity studies.

Chapter IV: Introduction and literature review of formazans, synthesis of formazan derivatives from N-ethylpiperazine, physical properties, spectral studies and microbial activity studies.

Chapter V: Overall results and conclusions.

Analysis

All the newly synthesized compounds have been studied by elemental and spectral analysis. Minimum Inhibitory Concentration (MIC) of all the synthesized compounds was determined against various strains of Gram Positive bacteria and Gram Negative bacteria for antibacterial activity. The comparison was made against standard drugs Gentamycin, Ampicillin, and Chloramphenicol by measuring zone of inhibition. Antifungal activity against C. *albicans* and A. *niger* were compared with standard drugs Clotrimazole, Miconazole Nitrate and Fluconazole by the same method.

The synthesized compounds are expected to exhibit moderate to good antimicrobial activity.

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